

Metabotropic glutamate receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [334]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate. The mGlu family is composed of eight members (named mGlu1 to mGlu8) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I (mGlu₁ and mGlu₅), Group-II (mGlu₂ and mGlu₃) and Group-III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈) (see Further reading).

transmembrane domain (TM), common to all GPCRs, is linked via a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. The structures of the VFTD of mGlu₁, mGlu₂, mGlu₃, mGlu₅ and mGlu₇ have been solved [190, 262, 255, 386]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organization similar to that of other GPCRs, although the helices appear more compacted [85, 415, 59]. mGlu form constitutive dimers crosslinked by a disulfide bridge. Recent studies revealed the possible formation of

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heterodimers between either group-I receptors, or within and between group-II and -III receptors [86]. Although well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [422, 257].

The endogenous ligands of mGlu are [L-glutamic acid](#), [L-serine-O-phosphate](#), N-acetylaspartylglutamate (NAAG) and [L-cysteine sulphonic acid](#). Group-I mGlu receptors may be activated by [3,5-DHPG](#) and [\(S\)-3HPG](#) [29] and antagonized by [\(S\)-hexylhomobotenic acid](#) [223]. Group-II mGlu receptors may be activated by [LY389795](#) [256], [LY379268](#) [256], [eglumegad](#) [337, 416], [DCG-IV](#) and [\(2R,3R\)-APDC](#) [338], and antagonised by [eGlu](#) [161] and [LY307452](#) [408, 100]. Group-III mGlu receptors may be activated by [L-AP4](#) and [\(R,S\)-4-PPG](#) [125]. An example of an antagonist selective for mGlu receptors is [LY341495](#), which blocks mGlu₂ and mGlu₃ at low nanomolar concentrations, mGlu₈ at high nanomolar concentrations, and mGlu₄, mGlu₅, and mGlu₇ in the micromolar range [176]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Contents

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mGlu₈ receptor

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=296>

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